Laparoscopic versus open major hepatectomy: a systematic review and meta-analysis of individual patient data

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Abstract

Background: The role of laparoscopy for major hepatectomies remains a matter of development and to be further assessed. The purpose of this study is to compare the short- and long-term outcomes between laparoscopic and open major hepatectomies meta-analyzing individual patient data from published comparative studies.

Methods: All retrospective studies comparing between laparoscopic and open major hepatectomies published until March 2017 were independently identified by two reviewers by searching in PubMed and Cochrane Central Register of Controlled Trials. Individual patient data were sought from all selected studies. Postoperative outcomes, including intraoperative blood loss, operative time, hospital stay, postoperative complications, mortality rates, and long-term survival were analyzed.

Results: A total of 917 patients were divided into the laparoscopic (427) and open (490) groups from eight selected studies. The hospital stay was significantly shorter, and the total morbidity was lower in the laparoscopic group. When classified by severity, the incidence of postoperative minor complications was lower; however, that of major complications was not significantly different. The operative time was longer in the laparoscopic group; however, intraoperative blood loss, perioperative mortality, and blood transfusions were comparable between the two groups. The overall survival in the patients with colorectal liver metastases and hepatocellular carcinoma was not significantly different between the two groups.

Conclusions: Laparoscopic major hepatectomies offer some perioperative advantages, including fewer complications and shorter hospital stay, without increasing the blood loss volume and mortality. Whether these results can anticipate the outcomes in future randomized controlled trials would be an interesting evidence to search for.

Introduction

Despite an initial cautious implementation in clinical practice, laparoscopic liver resections (LLRs) are now widely adopted for the treatment of benign and malignant diseases. [1-3] Benefits over the standard open technique have been reported by a large number of studies, particularly for laparoscopic left lateral sectionectomies and minor LLRs. [4-11]

However, laparoscopic major hepatectomies (LMHs) have been limited to tertiary referral centers and highly skilled surgeons owing to the associated technical demands. Although some series have shown that LMHs are associated with shorter hospitalization, fewer complications, decreased blood loss volume, and similar operative costs, others failed to document clear additional benefits over the open approach. [12-23] Randomized controlled trials would play a critical role by providing optimal levels of evidence on the actual benefit of laparoscopy for liver resections. Accordingly, the ORANGE 2 PLUS Trial is steadily recruiting patients undergoing LMHs or open major hepatectomies (OMHs). [24] Meanwhile, alternative evidence is desirable for best-practice recommendations. In preparation for the European Guidelines on Laparoscopic Liver Surgery, which took place in Southampton in February 2017, a systematic review and meta-analysis on LMH versus OMH was performed. [25] To ensure a high-quality meta-analysis, the individual patient data (IPD) of the selected published comparative studies were sought from all centers. Analyzing original raw data is considered to be the gold standard, offering significant advantages over analyzing published data. [26] The IPD approach has the potential to minimize publication and reporting bias, while allowing a detailed data checking and verification. [27] This study aimed to provide the first systematic review and meta-analysis using IPD on LMH versus OMH focusing on perioperative and oncological outcomes.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. [28]

Data sources and searches

All retrospective studies reporting on LMH published until March 2017 were identified by searching on PubMed and Cochrane Central Register of Controlled Trials. The keywords [(“laparoscopic” OR “laparoscopy”) AND (“major hepatectomy” OR “major liver resection” OR “right hepatectomy” OR “right hemihepatectomy” OR “right liver resection” OR “left hepatectomy” OR “left hemihepatectomy” OR “left liver resection” OR “major hepatectomies”)] were selected to identify all reports possibly related to LMH. The database search was supplemented with manual searches of the reference lists of the articles gathered.

Study selection

All retrospective studies comparing between LMH and OMH were selected. The inclusion criteria were as follows: (1) studies comparing between LMH and OMH, defined as right hepatectomy or left hepatectomy according to the Brisbane 2000 Nomenclature [29]; (2) studies reporting on benign and/or malignant disease with a clear description of the indications; (3) studies reporting on the perioperative short-term outcomes with a clear description of the results; and (4) studies including at least 20 patients who underwent LMH to limit the instability of the analysis potentially arising from the small study size. Review articles, case reports, letters, editorials, nonhuman studies, and non-English language studies were excluded. In addition, the exclusion criteria were as follows: (1) prior studies published by the same author or institution, including similar patient data, to include only the most recent data; (2) multicenter studies to avoid duplication of patients from the same institution; (3) studies reporting on minimally invasive techniques for major hepatectomy other than pure laparoscopic approaches (e.g., hand-assisted, hybrid techniques, laparoscopic-assisted, single-site incision, robotic, and donor hepatectomies); and (4) studies focused selectively on hepatolithiasis because of differences in patient backgrounds. Raw data of the selected studies were centrally collected, checked, reanalyzed, and combined.

Outcome measures, data extraction, and quality assessment

The meta-analyses were based on the IPD and updated data submitted by the corresponding author of the selected studies.

The outcomes of interest were as follows: operative time, intraoperative blood loss, blood transfusion rate, postoperative complications (total, minor, and major), perioperative mortality, hospital stay, and overall survival (OS). Complications were classified on the basis of Clavien-Dindo grade (minor < grade III; major ≥ grade III). The following patients' baseline characteristics were summarized: age, sex, tumor size, operation type, and diagnosis (Tables 1 and 2). All data were independently extracted by two reviewers (MK and FC). Any disagreement was resolved through a discussion between the two reviewers and the senior author (MAH) until a consensus was reached. The quality of the studies was assessed using a modified Newcastle-Ottawa Scale (NOS), which was developed for nonrandomized studies considered for systematic reviews and meta-analyses. [30]

Statistical analyses

The meta-analysis was performed using R (version 3.1.1; the R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$, with 95% confidence intervals (CIs) shown for all results.

A "two-stage" approach was adopted for the IPD meta-analyses, as recommended; the IPD within studies generated summary measures, which were combined using standard meta-analytical methods. The fixed-effects model was adopted if heterogeneity was not statistically significant. The random-effects model was used when statistical heterogeneity was identified. The mean difference (MD) in continuous variables was compared using the inverse variance method, and categorical dichotomous variables were assessed using risk differences (RDs) by the inverse variance method. OS was assessed using the hazard ratio (HR), which was calculated using the Cox proportional hazard model. Heterogeneity was assessed using Cochran's Q test; the observed values of I^2 were used to represent the severity of heterogeneity and were interpreted using thresholds that were previously recommended (0%–40%: likely minimal; 30%–60%: likely moderate; 50%–90%: likely substantial; and 75%–100%: likely considerable), along with the strength of evidence (*P*-values of < 0.1 were set for significance). [31]

Funnel plots were used to explore the presence of publication bias visually, and their symmetry was evaluated.

Results

The initial literature search yielded 418 studies reporting on LMH. Figure 1 illustrates the selection process.

All retrospective studies comparing between the laparoscopic and open approach for major hepatectomies were selected in accordance with the inclusion criteria (n = 13). [12-23] As two institutions had published two consecutive articles with duplication of patients, only the most recent article was considered. [10, 11] The 11 retained articles had a retrospective design and were published between 2009 and 2017. Among them, the full raw data were not retrieved for three studies. [13, 22, 23] As such, the eight remaining studies were included in the meta-analysis with IPD (Table 1). [14-21] No disclosure of results from any prospective, randomized, controlled trial was identified.

A total 917 patients were included in the meta-analysis (LMH: n = 427; OMH: n = 490). The total number of patients per study ranged from 40 to 211. The rate of conversion to open or laparoscopy-assisted surgery ranged from 9% to 42%, with 69 conversions in total (17.7%). All converted cases were included in the laparoscopic group, according to the intention-to-treat principle.

Operative procedures and indications are shown in Table 2. Five of the eight studies included patients with both malignant and benign diseases. [14, 15, 17-19] One study focused on colorectal liver metastases (CRLM), and two focused on hepatocellular carcinoma (HCC). [16, 20, 21] Five studies reported on mid- and long-term oncological outcomes. [14,16,17,20,21] The NOS scores ranged between 5 and 9 for all the identified studies (Table 3).

Operative time

The meta-analysis of eight studies showed a longer operative time in the LMH group (Fig. 2-1; MD, 50.82 min; 95% CI, 2.22–99.42 min; $P = 0.040$). [14-21] The importance of heterogeneity among the studies was considerable (I^2, 94.5%; $P < 0.1$).

Intraoperative blood loss

The meta-analysis of eight studies showed no significant difference in blood loss between the LMH and OMH groups (Fig. 2-2; MD, −49.17; 95% CI, −136.52 to 38.18 mL; $P = 0.269$). [14-21] The importance of heterogeneity among the studies was substantial (I^2, 74.2%; $P < 0.1$).

Blood transfusions

The meta-analysis of seven studies showed no significant difference in the blood transfusion rate between the LMH and OMH groups (Fig. 2-3; RD, 0.05; 95% CI, −0.03 to 0.13; $P = 0.223$). [14-17,19-21] The importance of heterogeneity among the studies was substantial (I^2, 77.5%; $P < 0.1$).

Hospital stay

The meta-analysis of eight studies showed a shorter postoperative hospitalization in the LMH group, which was 3.09 days shorter than that in the OMH group (Fig. 2-4; 95% CI, −4.96 to −1.22 days; $P = 0.001$). [14 -21] The importance of heterogeneity among the studies was substantial (I^2, 72.4%; $P < 0.1$).

Postoperative overall morbidity

The meta-analysis of eight studies showed a lower postoperative morbidity rate in the LMH group (Fig. 2-5; RD, −0.11; 95% CI, −0.17 to −0.05; $P < 0.001$). [14 -21] The importance of heterogeneity among the studies was minimal (I^2, 26.6%; $P > 0.1$).

Postoperative minor complications

The meta-analysis of eight studies showed a lower rate of minor complications in the LMH group (Fig. 3-1; RD, −0.07; 95% CI, −0.11 to −0.02; $P = 0.009$). [14 -21] The importance of heterogeneity among the studies was moderate (I^2, 40.8%; $P > 0.1$).

Postoperative major complications

The meta-analysis of eight studies showed no significant difference in the postoperative major morbidity rates between the LMH and OMH groups (Fig. 3-2, RD, −0.03; 95% CI, −0.07 to 0.01 $P = 0.093$). [14 -21] The importance of heterogeneity among the studies was minimal (I^2, 18.4%; $P > 0.1$).

Perioperative mortality

The meta-analysis of eight studies showed no significant difference in the perioperative mortality rates between the LMH and OMH groups (Fig. 3-3; RD, 0.0; 95% CI, −0.02 to 0.02; $P = 0.968$). [14 -21] Postoperative death occurred in eight patients who underwent LMH: one developed acute respiratory failure from pneumonia; one had cardiac failure; one had sepsis from bile leak; one had pulmonary embolism; two died from bleeding; and two developed liver failure. Six patients who underwent OMH also died: one had stroke; one had severe acute respiratory distress syndrome; three had liver failure; and the last one did not have details regarding death. The importance of heterogeneity among the studies was minimal (I^2, 0%; $P > 0.1$).

Long-term survival for CRLM and HCC

Five studies included the OS for CRLM, HCC, or both. A total of 119 patients had CRLM (OMH, 65; LMH, 54), and 252 patients had HCC (OMH, 166; LMH, 86). [14,16,17,20,21] No significant difference in the OS was observed between LMH and OMH among the patients with CRLM (Figs. 3 and 4; HR, 0.92; 95% CI, 0.44–1.92; $P = 0.834$). The importance of heterogeneity among the studies was minimal (I^2, 10.6%; $P > 0.1$). Similarly, no significant difference in the OS was observed between LMH and OMH among the patients with HCC (Figs. 3-5; HR, 0.98; 95% CI, 0.423–2.27; $P = 0.962$). The importance of heterogeneity among the studies was minimal (I^2, 0%; $P > 0.1$).

Publication bias

Funnel plots were drawn for each outcome and assessed for symmetry. The funnel plots of the publications were not asymmetrical, suggesting no or limited publication bias (Fig. 4).

Discussion

This meta-analysis reports on the comparative outcomes of LMH and OMH, providing the highest possible level of evidence in the absence of randomized trials. The meta-analysis exploited IPD from the nonrandomized comparative studies available for an advanced analysis of outcomes, thus optimizing the conclusions inferable from the present literature. The meta-analysis shows that the incidence of severe complications and mortality in LMH were comparable to those observed in OMH. It also highlights the association of the laparoscopic approach with some postoperative clinical advantages, albeit acknowledging the potential selection bias and study limitation due to retrospective nature of the studies included

The most important concern regarding any new surgical approach is the patient's safety, and this meta-analysis showed no significant difference in the perioperative mortality between LMH and OMH. Moreover, it was demonstrated that the blood transfusion rates and operative blood loss were comparable between them. These results corroborate the safety of these procedures and are consistent with the results disclosed by the majority of the studies, although some of them reported a reduction in the blood loss volume. [15,17,19] To date, the hemostatic effect of the intra-abdominal pressure induced by the pneumoperitoneum and the magnified view in laparoscopy may allow surgeons precise identification and management of vasculobiliary structures in cases of minor liver resections. [32,33] However, the inconsistency and variability in reporting blood loss and transfusion rates in different studies may justify the significant heterogeneity documented for those parameters in our meta-analysis. As such, it cannot be excluded that the treatment effect is underestimated, and that laparoscopy effectively confers advantages in terms of blood loss and transfusion rates for major liver resections or vice versa.

Concerning the feasibility of LMH, laparoscopic surgery has been assumed to require a longer operative time than open surgery. [34] Indeed, this meta-analysis demonstrated significant differences in the operative time between LMH and OMH and corroborates the results reported by the majority of the previous series that compared laparoscopic surgery with open surgery. [14,16, 19, 21] However, LMH was found to be only 50 min longer than open procedures, a difference that is believed to have a minor impact on the clinical outcomes after surgery. In addition, it is of a critical importance to note that those registered operative times have included all procedures performed during the learning curve for LMH in all centers. This also explains the 17.7% conversion rate (range, 9%–42%) observed in our study. This conversion rate is clearly higher than the average rates reported for a minor LLR and reasonably reflects the higher technical demands in these procedures. However, conversion may decrease the potential benefit of laparoscopy and be associated with higher complication rates than laparoscopically completed cases. Recent studies have emphasized the need to avoid conversions by adopting a stepwise approach when introducing a laparoscopic liver surgery and to consider conversion in the early stage of procedures if technical difficulty is encountered. [35,36] Our results confirm the technical challenges of LMH and strengthen the call for caution when starting a laparoscopic liver surgery. A number of difficulty scores, including new comprehensive scores have been recently published, and may serve as a clear guidance to surgeons when introducing the laparoscopic approach in their daily practice [37-40].

Intraoperative blood loss is the predominant cause of conversion in most series. [36,41] This is expected, since LMH often requires hilar dissection, preparation of the hepatic veins near the inferior vena cava, and long and complex parenchymal transection. Good dissection and careful vascular control are essential pillars to decrease these complications, thus requiring long experience and a steep learning curve. [42-44]

A shorter hospitalization was observed for LMH. Moreover, the meta-analysis reports a lower incidence of postoperative complications, particularly minor complications, whereas the incidence of major morbidity was similar between LMH and OMH. Interestingly, the results disclosed separately by most of the studies were not consistent on these aspects. Indeed, half of the studies have reported a hospital stay comparable to OMH without a significant advantage for LMH; hence, no precise conclusions could be withdrawn due to the differences in postoperative management and insurance policies in different countries and institutions. [16,18-20] Moreover, all except three studies reported no advantage in the total morbidity for LMH, and few studies specifically reported on minor complications with heterogeneity of outcomes. [16,17,19] A meta-analysis of a higher number of patients and the IPD approach was essential to calculate a more sensitive analysis and reach more definitive results on the total and minor morbidities. It was expected that the application of a minimally invasive approach can have an impact on reducing major complications. However, the meta-analysis failed to confirm this, and it is likely that the magnitude of a major liver resection remains considerable and that it continues to have a serious influence on outcomes even when a laparoscopic approach is used. Conversely, a possible impact of the learning curve may have led to a dilution of the treatment effect. Previous studies have suggested that at least 45 patients are required to overcome the learning curve [43,44]. Unfortunately, the majority of the studies reported have included patients undergoing surgery during the learning curve. As such, we believe that future assessments analyzing later experiences of LMH are needed.

Malignancies, particularly CRLM and HCC, are reportedly the most common indications for LMH. [45] Therefore, oncological efficiency is of a paramount importance in these procedures. Previous meta-analyses have demonstrated that minor LLRs are equivalent to open surgeries in terms of long-term survival for malignancy cases. [7,8,34] Our meta-analysis confirms that these results are also established for LMH, as there were no differences between the two groups regarding the long-term survival in both CRLM and HCC cases. However, it must be noted that we identified only five studies that reported on the long-term outcomes of LMH (CRLM, 119; HCC, 252). [14,16,17,20,21] Thus, larger studies, possibly randomized controlled trials, would be ideal to verify these findings.

The results herein have been compared with those reported in the comprehensive meta-analyses, including minor and major liver resections, conducted by Ciria et al. [46] Both meta-analyses exhibited a high profile of safety and efficacy for LMH, without disadvantages related to the minimally invasive approach from both the clinical and oncological points of view compared with those for OMH. While these meta-analyses confirmed that LMH is associated with shorter hospitalization, lower morbidity, and transfusion rates similar to that in OMH, they differently reported that the operative time was similar and estimated that the blood loss volumes were lower for LMH. We believe that these relative discrepancies from our meta-analyses can be explained by the use of IPD and slightly different inclusion criteria. In fact, our calculations were restricted to studies that included at least 20 patients without duplication, since it was assumed that LMH requires a steep learning curve and that small or duplicated studies should be excluded to optimize the synthesis and consequent conclusions. Additionally, a large study accounting for nearly half of the patients included by Ciria et al. (450 out of 859) was not considered, as the raw data were not available when requested. [12,46] Considering the favorable results reported by Martin et al. in terms of operative time and blood loss, together with the magnitude of the casuistry, we believe that this could have had a significant impact on their final outcomes. [12]

Limitation

However, the present meta-analysis had a few limitations that warrant consideration when interpreting the results. First, each study was a retrospective and nonrandomized study, indicating that unmeasured confounding factors and selection bias may have influenced the outcomes of these studies. Second, each institution might have performed surgeries and managed postoperative treatments according to different local policies. This may have a reasonable influence on the perioperative outcomes, particularly operative time and hospitalization. Third, this meta-analysis focused on the comparison of a limited number of perioperative variables (i.e., blood loss, blood transfusion requirement, operative time, morbidity, mortality, and hospitalization). These factors were selected because they represent the most common and reproducible parameters reported. Additional evaluations on the techniques adopted for liver resection, length of intensive care unit stay, and readmission rates would have added useful information to the present meta-analysis. However, these were not uniformly measured in the majority of the studies. Fourth, the present study included only high-volume laparoscopic liver surgery centers. Although we demonstrated several advantages of LMH, it is unclear whether these benefits would be applicable to low-volume centers because laparoscopic liver surgery requires a steep learning curve. Fifth, there were differences in the number of patients included in each study. The majority of the LMH cases were obtained from the study by Nomi et al. (n=183 among the total of 427 patients), while the majority of the OMH cases were obtained from the study by Ratti et al. and Yoon et al. (n=147 and n =115 among the total of 490 patients, respectively).[18,19,21] The results may be influenced by such institutions or surgeons who performed LMH and OMH. Lastly, the patients underwent laparoscopic surgery within the period of the learning curve of each center as mentioned previously, and it is expected that the results would be different if the cases considered were performed by surgeons who had gained full proficiency on LMH.

Although a number of meta-analysis on laparoscopic liver surgery have been reported, this is the first meta-analysis reporting on LMH versus OMH using IPD and their long-term outcomes. The IPD method helped reveal more details regarding the clinical outcomes and reduce the several biases to verify the results of each selected study. We further meta-analyzed the complication rates stratified by their severity. This insight would not have been possible with a standard meta-analysis of published data and would not have clarified that the reduction of the postoperative morbidity for LMH is mainly related to a decrease in the minor morbidity rather than in the major morbidity. Moreover, by meta-analyzing the long-term oncologic outcomes of patients with CRLM and HCC, we can more strongly support the oncologic validity of LMH, which has already been reported by a number of comparative studies. [33,47,48]

Conclusion

Our results suggest that LMH can be performed safely without increasing severe morbidity and mortality compared with their open counterparts. LMH also seem to be associated with clinical benefits such as less minor complication rate when performed at high-volume centers with advanced techniques and experience in minor LLR. However, these benefits should be interpreted with considerable caution due of the selection bias, differences in study design, and limitation herein discussed. Larger comparative studies of high-quality design and prospective randomized controlled trials are still needed to assess the short- and long-term outcomes of LMH as primary endpoints.

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Figure legends

Figure 1. Flow chart of the screening and selection process for the included studies

Figure 2-1. Forest plots of the operative time reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; MD, mean difference; W, weight; Z, Z statistics.

Figure 2-2. Forest plots of intraoperative blood loss reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; MD, mean difference; W, weight; Z, Z statistics.

Figure 2-3. Forest plots of the blood transfusion rates reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; RD, risk difference; W, weight; Z, Z statistics.

Figure 2-4. Forest plot of hospital stay reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; MD, mean difference; W, weight; Z, Z statistics.

Figure 2-5. Forest plots of the overall complication rates reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; RD, risk difference; W, weight; Z, Z statistics.

Figure 3-1. Forest plots of the minor complication rates reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; RD, risk difference; W, weight; Z, Z statistics.

Figure 3-2. Forest plots of the major complication rates reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMR, LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; RD, risk difference; W, weight; Z, Z statistics.

Figure 3-3. Forest plot of the perioperative mortality rates reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; SD, standard error; RD, risk difference; W, weight; Z, Z statistics.

Figure 3-4. Forest plot of the HR for the OS of the CRLM rates reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; CRLM, colorectal liver metastasis; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; OS, overall survival; SD, standard error; HR, hazard ratio; seTE, standard error of treatment effect; W, weight; Z, Z statistics.

Figure 3-5. Forest plot of the HR for the OS of the HCC rates reported in the included studies for the MAP

MAP, meta-analysis using individual patient data; CI, confidence interval; HCC, hepatocellular carcinoma; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; OS, overall survival; SD, standard error; HR, hazard ratio; seTE, standard error of treatment effect; W, weight; Z, Z statistics.

Figure 4. Funnel plot of each outcome reported in the included studies

MD, mean difference; RD, risk difference.

Tables

Table 1. Patient characteristics from the included studies

Author	Year	Country	Study design	No. of patients		Age, mean (SD)		Sex (M:F)		Maximum Tumor Size (mm), mean (SD)		Conversion (%)
				LMH	OMH	LMH	OMH	LMH	OMH	LMH	OMH	
Abu Hilal et al.[14]	2013	UK	RM	38 (45%)	46 (55%)	58.9 (15.6)	63.2 (12.9)	20:18	19:27	49.6 (29.2)	36.0 (33.3)	7 (19)
Dagher et al.[15]	2009	France	RM	22 (30%)	50 (70%)	60.9 (13.5)	61.1 (14.4)	13:9	25:25	42.7 (20.8)	36.0 (33.3)	2 (9)
Komatsu et al.[16]	2015	France	RM	38 (50%)	38 (50%)	61.5 (12.2)	61.7 (16.1)	33:5	34:4	66.5 (39.2)	92.1 (47.5)	13 (26)
Medbery et al.[17]	2014	USA	RM	48 (46%)	57 (54%)	51.9 (5)	57.0 (12.4)	19:29	23:34	59.1 (34.7)	79.9 (65.9)	5 (10.4)
Nomi et al.[18]	2015	France	R	183 (86)	28 (14%)	64 (10.4)	NR	107:76	NA	NR	NR	21 (11.5)

Ratti et al.[19]	2015	Italy	RM	49 (25%)	147 (75%)	59 (8)	62 (4)	23:26	70:77	50.3 (33.3)	60.4 (39.1)	13 (26)
Topal et al.[20]	2012	Belgium	RM	20 (50%)	20 (50%)	59.7 (12.5)	61.5 (10.8)	10:10	8:12	40.4 (17.5)	60.4 (39.1)	5 (25)
Yoon et al. [21]	2016	Korea	RM	37 (24%)	115 (76%)	55.2 (7.12)	58.4 (9.89)	26:11	93:22	31.3 (16.2)	58.4 (44.8)	NR

F, female; LMH, laparoscopic major hepatectomy; M, male; NR, not reported; OMH, open major hepatectomy; R, retrospective study; RM, retrospective matched study; SD, standard deviation.

Table 2. Summary of the procedure and diagnosis in the studies

Study	Type of major hepatectomy		Indication		Long-term outcome
	LMH, *n*	OMH, *n*	LMH, *n* (%)	OMH, *n* (%)	LMH vs. OMH
Abu Hilal et al.[14]	LRH, 38	ORH, 46	CRLM, 20 (53) HCC, 4 (11) Others, 14 (37)	CRLM, 34 (75) HCC, 5 (11) Others, 7 (14)	81.5% vs. 65.5%; *P* = 0.14 (3-year overall survival)
Dagher et al.[15]	LRH, 22	ORH, 50	CRLM, 10 (45.5) HCC, 4 (18) Other malignancy, 1 (4.5) Benign, 7 (32)	CRLM, 23 (46) HCC, 10 (20) Other malignancy, 3 (6) Benign, 14 (28)	NR
Komatsu et al.[16]	LRH, 28 LLH, 10	ORH, 28 OLH, 10	HCC, 38 (100)	HCC, 38 (100)	73.4% vs. 69.2%; *P* = 0.951 (3-year overall survival)
Medbery et al. [17]	LRH, 48	ORH, 57	CRLM, 14 (29) HCC, 6 (13) Others, 28 (58)	CRLM, 18 (32) HCC, 8 (14) Others, 31 (54)	85.4% vs. 77.2%; *P* = 0.185 (5-year overall survival)
Nomi et al. [18]	LRH, 122 LLH, 29 Others, 22 [a]	ORH, 13 OLH, 15	CRLM, 123 (67) HCC, 20 (11) Others, 40 (22)	CRLM, 10 (36) HCC, 3(10) Other, 15 (54)	NR

Ratti et al. [19]	LRH, 30 LLH, 19	ORH, 84 OLH, 63	CRLM, 23(46.9) HCC, 10 (20.4) Others, 16 (32.7)	CRLM, 59 (40.1) HCC, 36 (24.5) Others, 52 (35.4)	NR
Topal et al. [20]	LRH, 13 LLH, 4 Others, 3 [b]	ORH, 7 LLH, 6 Others, 7	CRLM, 20 (100)	CRLM, 20 (100)	48% vs. 46%; *P* = 0.872 (5-year overall survival)
Yoon et al. [21]	LRH, 37	ORH, 115	HCC, 37 (100)	HCC, 115 (100)	85.1% vs. 83.9%; *P* = 0.645 (2-year disease-free survival) 100% vs. 88.8%; *P* = 0.090 (2-year overall survival)

CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; LLH, laparoscopic left hepatectomy; LMH, laparoscopic major hepatectomy; NR, not reported; LRH, laparoscopic right hepatectomy; OLH, open left hepatectomy; OMH, open major hepatectomy; ORH, open right hepatectomy; others, liver resection of more than three segments.

a Left trisectionectomy, 11 (6%); right trisectionectomy, 13 (7.1%); and central hepatectomy, 8 (4.4%).

b Non-anatomical liver resection (more than three segments).

Table 3. Assessing the quality of the nonrandomized studies using the Newcastle-Ottawa Scale

Study	Selection				Comparability	Outcome			Score
	Representativeness of the laparoscopic group	Selection of the open group	Exposure	Outcome of interest not present at the start	Comparability between laparoscopic and open	Assessment of outcome	Follow-up	Adequacy of follow-up of the cohort	Score
Abu Hilal et al.[14]	Yes	Same	Surgical records	Yes	Unsuitable for laparoscopic resection as the tumor was within 2 cm of a major vessel. Matching for only right hepatectomy.	Record linkage	3 years	Unclear	8

Dagher et al.[15]	Yes	Same	Surgical records	Yes	Laparoscopy excluded for a large tumor (>8 cm), vascular invasion; Child-Pugh score B, C, ASA score > 4; and subcapsular invasion. Matching for age, ASA score, sex, BMI, tumor size, and liver disease	Record linkage	90 days	Unclear	8
Komatsu et al.[16]	Yes	Same	Surgical records	Yes	Restricted HCC with absence of extrahepatic metastasis and curative hepatectomy. Matching for age, sex, BMI, ASA score, Child-Pugh score, tumor size, tumor numbers, and operative procedure	Record linkage	3 years	Unclear	8

Medbery et al.[17]	Yes	Same	Surgical records	Yes	No restriction. Matching for only right hepatectomy	Record linkage	5 years	Unclear	8
Nomi et al.[18]	Yes	Same	Surgical records	Yes	Decision by the hepatobiliary multidisciplinary team. No matching	Record linkage	90 days	Unclear	5
Ratti et al.[19]	Yes	Same	Surgical records	Yes	Propensity score matching with six covariates [a]	Record linkage	90 days	Unclear	8
Topal et al.[20]	Yes	Same	Surgical records	Yes	Restricted to CRLM. Matched 13 baseline characteristics, including age, ASA score, and location tumor [b]	Record linkage	5 years	Every 3 and 4 months on CT or MRI	9

Yoon et al.[21]	Yes	Same	Surgical records	Yes	Propensity score matching on nine covariates [c]	Record linkage	5 years	Every 3 months on CT or MRI	9

ASA, American Society of Anesthesiologists; BMI, body mass index; CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; CT, computed tomography; MRI magnetic resonance imaging.

[a] ASA score, previous abdominal surgery, previous interventional procedures, indication, lesion size, and associated procedures.

[b] Age, sex, location of tumor, ASA score, repeated hepatectomy, simultaneous colorectal resection, simultaneous local ablation therapy, before or after chemotherapy, and before or after biotherapy.

[c] Age, sex, history of HCC, preoperative level of tumor markers (AFP, PIVKA-II), tumor number and size, resection margin, and presence of lymphovascular invasion.